Electronically filed

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No. 6,852,522 B1

Issued: February 8, 2005

Patentee: Palese *et al.*

For: NOVEL METHODS AND INTERFERON DEFICIENT SUBSTRATES FOR THE PROPAGATION OF VIRUSES

Application No. 09/724,419

Filed: November 28, 2000

Attorney Docket No. 6923-102-999

REQUEST FOR CERTIFICATE OF CORRECTION

Commissioner for Patents
ATTN: Certificate of Correction Branch
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 C.F.R. § 1.322, the Patentee hereby requests the issuance of a Certificate of Correction in connection with the above-identified patent. A Certificate of Correction setting forth the necessary correction is submitted herewith. Claim 9 in the issued patent incorrectly recites " . . . amino acid residues 1-10 . . . ." Patentee requests that claim 9 be amended to recite " . . . amino acid residues 1-110 . . . ." In support of its request, Patentee submits herewith a copy of an Amendment, filed February 26, 2004, which contains a listing of the claims which were allowed pursuant to the Notice of Allowability mailed May 27, 2004.

Patentee respectfully submits that no fee is required for this Request because the error was incurred through error of the Patent Office. However, if any fee is deemed necessary, please charge such fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: April 20, 2009

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Enclosures

PRINTER'S TRIM LINE

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	6,852,522
DATED	:	February 8, 2005
INVENTOR(S)	:	Peter Palese Adolfo Garcia-Sastre Robert O'Neill

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 32, line 2, replace "amino acid residues 1-10" with -- amino acid residues 1-110 --.

MAILING ADDRESS OF SENDER:
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FORM PTO 1050

PATENT NO. 6852522

No. of add'l. copies @ 30¢ per page

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Palese *et al.*		Confirmation No.:	9897
Serial No.	09/724,419	Art Unit:	1651
Filed:	November 28, 2000	Examiner:	Lankford, Jr. Leon B.
For:	NOVEL METHODS AND INTERFERON DEFICIENT SUBSTRATES FOR THE PROPAGATION OF VIRUSES	Attorney Docket:	6923-102

AMENDMENT UNDER 37 C.F.R. § 1.116

Mail Stop AF
Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In response to the final Office Action mailed August 26, 2003, and in accordance with Rule 116 of the Rules of Practice, please enter and consider the remarks and amendments below intended to put this application into form for allowance. Applicants submit herewith: (a) a Petition For Extension Of Time (in duplicate), accompanied by the appropriate provision authorizing payment of the required fee; (b) an Amendment Fee Transmittal (in duplicate), accompanied by the appropriate provision authorizing payment of the required fee; (c) a Notice of Appeal from the Primary Examiner to the Board of Appeals and Interferences (in duplicate), accompanied by the appropriate provision authorizing payment of the required fee; (d) copies of the Supplemental Information Disclosure and revised PTO 1449 form filed on June 11, 2003; (e) Exhibit A, a copy of Express Mail Label No. EL 501 761 157 US; and (f) Exhibit B, a copy of the postcard returned to Applicants' attorneys.

It is estimated that no additional fee is required for filing this Amendment. However, should the Patent Office determine otherwise, please charge the necessary fee to Deposit Account No. 16-1150.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 4 of this paper.

Listing of Claims:

The listing of claims below will replace all prior versions, and listings, of claims in the application.

1-41. (Canceled)

42. (Currently amended) An embryonated egg ~~less than ten~~ six to eight days old containing a recombinantly engineered influenza virus having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to antagonize the cellular interferon response, wherein said virus is not influenza C virus.

43. (Canceled)

44. (Currently amended) An embryonated egg containing in the allantoic cavity an attenuated influenza virus having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to antagonize the cellular interferon response, wherein the embryonated egg is six to ~~nine~~ eight days old and said virus is not influenza C virus.

45. (Currently amended) An embyronated egg ~~less than 10~~ six to eight days old containing delNS1.

46. (Canceled)

47. (Currently amended) The embryonated egg of Claim ~~41 or~~ 42, 44 or 45, wherein the egg is a six ~~to nine days~~ day old chick egg.

48-49. (Canceled)

50. (Previously presented) The embryonated egg of Claim 42 or 44, wherein the attenuated influenza virus is engineered to encode an epitope derived from another virus.

51. (Previously presented) The embryonated egg of Claim 42 or 44, wherein the attenuated influenza virus has a segmented genome comprising at least one segment derived from a different virus.

52. (Previously presented) The embryonated egg of Claim 44, wherein the attenuated influenza virus is genetically engineered.

53. (Previously presented) The embryonated egg of Claim 42 or 44, wherein the mutation in the NS1 gene is a deletion at the C-terminal of NS1.

54. (Previously presented) The embryonated egg of Claim 53, wherein the NS1 gene encodes truncated NS1 proteins consisting of amino acid residues 1-60, amino acid

residues 1-70, amino acid residues 1-90, amino acid residues 1-99, amino acid residues 1-100, amino acid residues 1-110, amino acid residues 1-120, amino acid residues 1-124, or amino acid residues 1-130 of the wild-type NS1.

55. (Previously presented) The embryonated egg of Claim 42 or 44, wherein the mutation in the NS1 gene is a deletion at the amino-terminal of NS1.

56. (Previously presented) The embryonated egg of Claim 42 or 44, wherein the influenza virus is influenza A or B virus.

57. (Previously presented) The embryonated egg of Claim 42 or 44, wherein the mutation in the NS1 gene is responsible for the attenuated phenotype of the influenza virus.

58-71. (Canceled)

72. (Currently amended) The embryonated egg of Claim ~~41 or~~ 42, 44 or 45, wherein the egg is six to seven days old.

73. (Canceled)

74. (Previously presented) The embryonated egg of Claim 42 or 44, wherein the attenuated influenza virus is engineered to encode a foreign antigen.

75. (Canceled)

76. (Currently amended) The embyronated egg of Claim 42, ~~44~~ or 45, wherein the egg is six ~~to seven~~ days old.

77. (Canceled)

78. (Previously presented) The embryonated egg of Claim 42 or 44, wherein the attenuated influenza virus is engineered to encode a tumor antigen.

REMARKS

Claims 41-57 and 71-78 were pending in this application. In order to expedite the prosecution of the present application and without conceding to the validity of the Examiner's rejections, Applicants have canceled claims 41, 43, 46, 48, 49, 71, 73, 75 and 77, without prejudice to Applicants' rights to pursue the subject matter of the canceled claims in a related application, and have amended claims 42, 44, 45, 47, 72 and 76 to more particularly point out and distinctly claim the subject matter that Applicants regard as their invention. In particular, claims 42, 44 and 45 were amended to recite that the embryonated egg is six to eight days old. Claims 47, 72 and 76 have been amended to make the claims dependent from claims 42, 44 and 45. The amended claims are fully supported by the specification of the present application, see, *e.g.*, page 24, lines 11-18 and page 26, lines 3-7, and do not constitute new matter. Upon entry of this amendment, claims 42, 44, 45, 47, 50-57, 72, 74, 76 and 78 will be pending in the present application.

The amendments and remarks made herein narrow the issues on appeal and are designed to place the application into condition for allowance. Thus, Applicants respectfully request that the amendments and remarks made herein be entered and fully considered.

1. INFORMATION DISCLOSURE STATEMENT

Applicants note that the Supplemental Information Disclosure Statement ("IDS"), revised PTO 1449 form and references listed on the revised PTO 1449 form filed on June 11, 2003 in the United States Patent and Trademark Office ("USPTO") using "Express Mail Post Office to Addressee" service under Express Mail Label No. EV 335 855 811 US were not acknowledged in the Office Action Summary. For the Examiner's convenience, copies of the IDS and revised PTO 1449 form filed on June 11, 2003 in the USPTO are enclosed herewith. As evidence of the fact that the IDS, revised PTO 1449 form and references listed on the revised PTO 1449 form were filed on June 11, 2003 in the USPTO and received by the USTPO, Applicants enclose herewith: (1) Exhibit A, a copy of Express Mail Label No. EV 335 855 811 US with the "date-in" June 11, 2003 and "time-in" 06:50 and (2) Exhibit B, a copy of the postcard, which listed on one side the items filed on June 11, 2003 and Express Mail Label No. EV 335 855 811 US, returned to Applicants' attorneys stamped received by the USPTO with the date of June 11, 2003. Accordingly, pursuant to 37 C.F.R. § 1.10 (a), Applicants did, indeed, file the IDS, revised PTO 1449 form and references listed on the revised PTO 1449 form on June 11, 2003 in the USPTO

Applicants respectfully request that the Examiner consider References DE-DH listed on the revised PTO Form-1449 filed in the USPTO on June 11 2003. If any of these references cannot be located, please contact the attorneys for Applicants so that they may provide additional copies of the references.

2. THE REJECTION UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 41-57 and 71-78 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Mitsuhashi (U.S. Patent No. 4,659,569; "Mitsuhashi") and Sasaki (JP 59-39831; "Sasaki"). The Examiner contends that Mitushashi and Sasaki teach eggs infected with viruses, particularly influenza viruses, and that embryonated eggs less than 10 days old are susceptible to virus infection and replication. The Examiner admits that the references do not teach the specific viral strains claimed. See Office Action mailed August 26, 2003, at page 3, lines 10-11. Despite this admission, the Examiner alleges that the composition of the claimed invention would have been obvious to one of ordinary skill in the art at the time of the invention, because "it is notoriously old and well known in the art to propagate viruses in such eggs" and "one would have been motivated to make the composition because one would reasonably expect the infected egg to yield replicated virus." For the reasons detailed below, however, the rejection of claims 41-57 and 71-78 under 35 U.S.C. § 103(a) cannot stand and should be withdrawn.

A finding of obviousness requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1996). The proper inquiry is whether the art suggests the invention, and whether the art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell* 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicants' disclosure. *In re Vaeck* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In order to expedite the prosecution of the application and without conceding to the validity of the rejection, Applicants have amended claims 42, 44 and 45 (and claims

dependent therefrom) to recite an embryonated egg six to eight days old containing the specified attenuated influenza viruses. In particular, claim 42 has been amended to recite an embryonated egg six to eight days old containing a recombinantly engineered influenza virus having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to antagonize the cellular interferon response, wherein the virus is not influenza C virus. Claim 44 has been amended to recite an embryonated egg containing in the allantoic cavity an attenuated influenza virus having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to antagonize the cellular interferon response, wherein the embryonated egg is six to eight days old and the virus is not influenza C virus. Claim 45 has been amended to recite an embyronated egg six to eight days old containing delNS1.

None of the cited references, alone or in combination, teach or suggest the claimed invention, *i.e.*, an embryonated egg six to eight days old containing delNS1 or an attenuated influenza virus having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to antagonize the cellular interferon response. There is no recognition, suggestion or appreciation in Mitsuhashi to propagate influenza virus in embryonated eggs of a particular age, much less to propagate delNS1 or an attenuated influenza virus having a mutation in NS1 that diminishes or eliminates the ability of the NS1 gene product to antagonize the cellular interferon response in embryonated eggs six to eight days old. Mitsuhashi teaches the use of ten day old embryonated eggs for the propagation of influenza virus. Mitsuhashi does not teach using an embryonated egg less than ten days old for the propagation of influenza virus. Mitsuhashi only teaches the use of eight day old embryonated eggs to propagate Newcastle disease virus. Newcastle disease virus and influenza virus belong to different families of RNA viruses and have different characteristics from each other. For example, influenza virus belongs to the *Orthomyxoviraidae* family, has a segmented genome, has a diameter of 80-120 nm and replicates in the nucleus. In contrast, Newcastle disease virus belongs to the *Paramyxoviradae* family, has a non-segmented genome, has a diameter of about 150 nm and replicates in the cytoplasm. *See, e.g.*, Wolfgang K. Joklik *et al.*, Zinsser Microbiology, 656-657 (19th edition 1988). Thus, the propagation of Newcastle disease virus in embryonated eggs eight days old would not suggest or motivate one of skill in the art to propagate an influenza virus in embryonated eggs eight days old or less. In fact, the teaching in Mitsuhashi regarding the propagation of influenza virus would suggest or motivate one of skill in the art to use embryonated eggs ten days old to propagate influenza virus.

Sasaki relates to propagating a swine influenza virus in the allantoic cavity of an embryonated egg of 9-11 days of age. Sasaki does not teach or suggest an embryonated egg six to eight days containing an attenuated influenza virus having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to antagonize the cellular interferon response. In both Sasaki and Mitsuhashi, the propagation of influenza virus in embryonated eggs 9-11 or 10 days old, respectively, was sufficient for the preparation of influenza virus vaccines. Thus, neither teaching in Sasaki or Mitsuhashi would motivate one of skill in the art to produce an embryonated egg six to eight days old containing delNS1 or an attenuated influenza virus having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to antagonize the cellular interferon response.

Moreover, as of the effective filing date of the present invention, the accepted age for embryonated eggs as a growth substrate for growth and propagation of influenza virus was 10-12 days, and not embryonated eggs 6 to 8 days old, as claimed in the present invention. Immature embryonated eggs, such as six to eight day old eggs were *not* recognized by one of skill in the art as a substrate for growth and propagation of influenza virus, prior to the present invention. In light of the fragile condition, small allantoic cavity and small nucleus of these young eggs, the prevailing view of those skilled in the art was that they were particularly unattractive for growth and propagation of influenza virus. Accordingly, there would have been no motivation for one of skill in the art, given the state of the art as of the effective filing date of the present application to use an immature embryonated egg six to eight days old for growth and propagation of influenza virus.

Applicants were the first to teach that the introduction of mutations in the NS1 gene of influenza viruses diminishes or eliminates the ability of the NS1 gene product to antagonize the cellular interferon response (see, *e.g.*, the specification of the present application at page 14, line 23 to page 15, line 10; page 17, line 36 to page 18, line 12; and Example 6, page 38, line 7 to page 42, line 30). Further, Applicants were the first to teach that immature embryonated eggs (*e.g.*, six to eight day old embryonated eggs) provide a better growth substrate for an attenuated influenza virus having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to antagonize the cellular interferon response than older embryonated eggs (*e.g.*, 10 and 12 day old embryonated eggs) which are the conventional substrates for growth and production of influenza virus. In particular, Applicants demonstrated that an immature embryonated egg, especially its allantoic cavity, is an excellent growth substrate for attenuated influenza viruses having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to

antagonize the cellular interferon response. The cited art does not recognize or appreciate that immature embryonated eggs (*e.g.*, six day old eggs) are a better substrate for the propagation of attenuated influenza viruses having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to induce a cellular interferon response. It was Applicants' unexpected discovery that attenuated influenza viruses having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to induce a cellular interferon response grow to a higher titer in immature embryonated eggs that resulted in the recognition of immature embryonated eggs as a suitable substrate for the propagation of such viruses. Therefore, in view of the foregoing, immature embryonated eggs six to eight days old containing an attenuated influenza virus having a mutation in the NS1 gene that diminishes or eliminates the ability of the NS1 gene product to induce a cellular interferon response are not rendered obvious over the references cited by the Examiner.

In view of the foregoing, the rejections under 35 U.S.C. § 103(a) cannot stand and should be withdrawn.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing remarks. Applicants believe that all of the present claims meet all of the requirements for patentability. Withdrawal of all rejections is requested.

If any issues remain, the Examiner is requested to telephone the undersigned at (212) 790-6431.

Respectfully submitted,

Date: February 26, 2004

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